REMARKS/ ARGUMENTS

Claims 46, 48, 51-60 are pending in this application. Claim 49 has been canceled, and the limitation of canceled claim 49 has been included in claim 46.

Rejections under 35 U.S.C. §102

I. Claims 46, 48, 49, 51-58, and 60 were rejected under 35 U.S.C. §102(b) as being anticipated by Kjornaes et al. (U.S. Patent No. 4,713,248). Claim 49 has been canceled. Accordingly, rejection of claim 49 is moot. Reconsideration of the rejection of claims 46, 48, 51-58, and 60 is respectfully requested.

Claim 46 is independent and has been amended. Claims 48 and 51-58 depend from claim 46. Amended claim 46 recites a dosage form which comprises a formulation comprising a therapeutic agent, a first membrane in contact with the formulation, and a second membrane positioned over an outside surface of the first membrane. The second membrane is a semipermeable membrane that maintains its physical and chemical integrity as the dosage form dispenses the therapeutic agent. The first and second membranes are formed such that the first membrane exhibits a permeability responsive to changes in osmotic pressure. At least one passageway is formed across the membranes for dispensing the therapeutic agent from the dosage form.

The Kjornaes et al. patent teaches a dosage form having an active substance coated with a diffusion coating. The diffusion coating includes an inner layer that is made of a water-dispersible film-forming agent, e.g., ethylcellulose, and a polymer that delays and controls diffusion through the inner layer, e.g., hydroxypropylcellulose. The diffusion coating also includes an outer layer that is made of a film-forming agent with anti-adhesive properties and optional diffusion barrier properties, e.g., ethylcellulose or enteric coating.

The Kjornaes et al. patent does not anticipate the invention recited in amended claim 46 for a variety of reasons. First of all, the Kjornaes et al. patent does not disclose or teach at least one passageway formed across the membranes for dispensing the therapeutic agent from the dosage form. Rather, the Kjornaes et al. patent discloses or teaches a diffusion coating that

gradually lets the active substance pass through its layers (col. 3, lines 14-17). That the Kjornaes et al. patent did not anticipate forming a passageway across the diffusional coating is evident because, as a practical matter, the individual coated units being only 0.1 to 1.5 mm in size (col. 7, lines 41-42) are too small to consistently drill with any reliability in a high volume manufacturing process.

Secondly, the Kjornaes et al. patent does not disclose or teach a second membrane that is a semipermeable membrane that maintains its physical and chemical integrity as the dosage form dispenses the therapeutic agent. In the claimed invention, the semipermeable membrane allows passage of an aqueous or an aqueous-biological fluid but acts as a barrier to the passage of a therapeutic agent, forcing the therapeutic agent to be dispensed through the confines of the passageway formed across the membranes. In the Kjornaes et al. dosage form, in order for the active substance to be dispensed through the diffusion coating, the outer layer of the diffusion coating would either have to be permeable to the active substance or removable in the environment of use. The claimed invention relies on the second membrane being semipermeable and remaining in place over the outside surface of the first membrane while dispensing the therapeutic agent.

Further evidence that the diffusion coating of the Kjornaes et al. patent lacks semipermeable character can be seen in the reliance of the release mechanism of the Kjornaes et al. dosage form on buffering of the internal environment of the dosage form when delivering an active substance that has pH-dependent solubility (col. 8, lines 1-9). The inability to exclude ions present within the fluids of the gastrointestinal tract is clear evidence that the diffusion coating lacks a semipermeable character. Ions within the upper gastrointestinal tract create an acidic environment, while ions in the lower tract create an alkaline environment. The porous diffusion coating of the Kjornaes et al. patent allow such ions to diffuse from the biological environment into the internal environment of the dosage form. In the absence of a buffer system present within the dosage form, the diffusional release of the dosage form when dispensing drugs of pH-dependent solubility is utterly dependent upon the internal buffer.

Example 7 of the Kjornaes et al. patent discloses the use of a relatively large fraction of buffering material in the core of dosage forms in order to deliver a drug at similar rates in

simulated gastric fluid compared to simulated intestinal fluid. In this example, sodium dihydrogen phosphate is present at a level of 15 wt% and is used to maintain an acidic environment within the dosage form to keep the concentration of the drug from changing when the dosage form is in the upper gastrointestinal tract compared to the lower. Sodium dihydrogen phosphate is commonly used as an acidic buffer (Food Chemical Codex IV pg 374). The relatively high amount of buffer is needed because the diffusion coating of the Kjornaes et al. dosage form allows diffusional release of the buffer into the environment. In order for the buffer to be present for sufficiently long time and to prevent premature depletion, a substantial loading of 15 wt % is incorporated into core of the individual units. While the dosage form of the claimed invention may optionally employ internal buffers to increase the solubility of a lowly soluble drug, the dosage form of the claimed invention does not rely on the use of internal buffers to achieve equivalent release performance in low and high pH because that function is provided by the external semipermeable membrane.

Finally, the Kjornaes et al. dosage form is not formulated and configured to deliver the therapeutic agent in an extended, non-declining release profile. Rather, the Kjornaes et al. patent discloses release patterns that are declining. These declining patterns can be observed by careful examination of the release data in, for example, Examples 6 and 7 of the Kjornaes et al. patent. For illustration purposes, Appendix A shows plots of the release data in Examples 6 and 7 of the Kjornaes et al. patent. In these plots, the average release rate is plotted in bar graph form, and the corresponding cumulative release is plotted in line graph form. The upper frame represents the release performance of the potassium chloride dosage form (Example 6), while the lower frame represents the release of the propranolol dosage form (Example 7). The plots reveal declining release rate patterns. In both examples, the dosage forms present a fast release rate during the first two hours followed by a slow release rate during the subsequent four hours. During the first two hours of release approximately half of the claimed dose is released for both drugs. These patterns have shapes that are opposite to the patterns disclosed in the claimed invention, which are non-declining.

The membranes of the claimed invention achieve both constant release rate and ascending release rate patterns for prolonged time over many hours that are not anticipated by

the Kjornaes et al. patent since the release pattern of the Kjornaes et al. patent is declining. The Kjornaes et al. dosage form is incapable of a non-declining release rate pattern because the active substance is diffusing through the porous diffusion coating rather than streaming through a passageway formed across membranes under osmotic driving force. The porous diffusion coating of the Kjornaes et al. dosage form, whether made of a single or dual coating, is incapable of preventing premature elution of the active pharmaceutical excipient and therefore produce declining patterns of relatively short duration.

From the foregoing, it is clear that the Kjornaes et al. patent does not anticipate or make obvious the invention recited in claims 46, 48, and 51-58. Withdrawal of the rejection of these claims over the Kjornaes et al. patent is respectfully requested. Claim 60, which recites a method of administering the inventive dosage form of claim 46, is likewise patentable in view of the foregoing arguments.

II. Claims 46, 48, 49, 51-58, and 60 were rejected under 35 U.S.C. §102 as being anticipated by Chen et al. (U.S. Patent No. 5,558,879). Claim 49 has been canceled. Accordingly, rejection of claim 49 is moot. Reconsideration of the rejection of claims 46, 48, 51-58, and 60 is respectfully requested.

The Chen et al. patent discloses a dual membrane coating having a first inner coating layer and a second outer coating layer. The second outer coating layer includes a medicament and a water soluble polymer, e.g., hydroxypropylcellulose. In contrast, the first and second membranes of the claimed invention are composed of mostly water insoluble polymer and leachable water soluble polymers, respectively. When placed in water, the leachable component is sensitive to osmotic environment, thus changing the permeability of the membrane and the release profile of the dosage form. The first and second membranes of the claimed invention will exist always and will only be partially dissolved. The outer membrane of the Chen et al. patent dissolves always during operation.

The Chen et al. patent teaches a second outer coating layer that is water soluble for good reason. The passageway of the Chen et al. dosage form is formed in-situ and relies upon the rupture of the first inner coating layer. As the Chen et al. dosage form is placed in an aqueous

environment, the second outer coating layer rapidly dissolves and exposes the first inner coating layer. Water is then imbibed by osmosis across the membrane and into the core. As there is no preformed passageway in the Chen et al. dosage form, the incoming water causes a buildup of hydrostatic pressure. This hydrostatic pressure continues to build with time causing the first inner coating layer to stretch and eventually tear. The resulting tear serves as the passageway through which drug is subsequently pumped by osmotic action. Thus, the Chen et al. dosage form relies on a membrane coating that has poor tensile properties such that when under tension it ruptures in-situ.

According to Rowe, "The dependence of the mechanical properties (tensile strength, elongation) of polymers upon the molecular weight is qualitatively the same for all polymers. At low molecular weights they are relatively weak but as the molecular weight increases the strength also increases proportionally until at some critical molecular weight there is no further increase. This inflection in the curve occurs at a degree of polymerization equivalent to a molecular weight of approximately 4-5 x exp4 for ethylcellulose." (Rowe, R.C., "Molecular weight studies on ethylcellulose used in film coating", Acta Pharm. Suec. 19, 157-160 (1982)).

Rowe, *supra*, provides elongation at break data which is a measure of how prone to rupture under tension for different grades of ethylcellulose. The grade of ethylcellulose cited in the example in the Chen et al. patent has an ethoxy content of 48.0-49.5 wt%, a molecular weight of 10,500 grams per mole, and a viscosity of 9-11 centipoise. This is a very low molecular weight and corresponds to a relatively brittle material. This grade of ethylcellulose has an elongation break value of about 19%. Other grades having higher molecular weight than the ethylcellulose reported in the Chen et al. patent have elongation at break values on the order of 35%. Moreover, the membrane coat of the Chen et al. patent is further weakened by the presence of very high fraction of pore forming material. The example in the Chen et al. patent cites the membrane composition as having only 58.5 wt% of ethylcellulose (29.2 wt% of hydroxypropyl cellulose, 12.3 wt% triacetin).

The brittle forms of ethylcellulose coatings disclosed in the Chen et al. patent are consistent with the mechanism of the Chen et al. dosage form requiring a membrane that easily ruptures under tension. As such, the Chen et al. patent teaches away from the second membrane

layer of the claimed invention which maintains its physical and chemical integrity as the dosage form dispenses the therapeutic agent. In the present application, high-tensile cellulose acetate is given as an example of suitable material for the second membrane layer. The lowest molecular weight of cellulose acetate that is commercially available for pharmaceutical use is much higher than the Chen et al. polymer. It is 30,000 grams per mole (Eastman Cellulose Esters for Pharmaceutical Drug Delivery, Publication EFC-233C (October 1997)). The Chen et al. patent teaches a brittle membrane and therefore does not anticipate the tough second membrane of the present invention which maintains its physical and chemical integrity while the therapeutic agent is being dispensed from the dosage form.

From the foregoing, it is clear that claim 46 is not anticipated by the Chen et al. patent. Withdrawal of the rejection of claim 46 is respectfully requested. Claims 48 and 51-58, being dependent on claim 46, are likewise patentable in view of the foregoing arguments. Claim 60, which recites a method of administering the inventive dosage form recited in claim 46, is also patentable in view of the foregoing arguments.

III. Claims 46, 48, 49, and 51-60 were rejected under 35 U.S.C. §102 as being anticipated by Bartoo et al. (U.S. Patent No. 4,743,248). Claim 49 has been canceled. Accordingly, the rejection of claim 49 is moot. Reconsideration of the rejection of claims 46, 48, and 51-60 is respectfully requested.

The Examiner correctly recites that the Bartoo et al. device comprises an osmotic core, a bilayer membrane coating, and an orifice. However, the Bartoo et al. patent does not anticipate a first membrane layer with permeability that responds to osmotic pressure, as recited in the claims. Rather, the Bartoo et al. patent discloses a subcoat layer having a permeability that is sensitive to pH. The subcoat layer of the Bartoo et al. dosage form responds to changes in pH as a result of the biological fluid entering the system through the passageway of the dosage form in the opposite direction of the fluid flow of the drug. This process occurs after the functional lifetime of the dosage form when the fluid pumping out of the dosage form is negligibly low such that alkaline biological fluids can diffuse countercurrent through the passageway into the interior of the dosage form and subsequently react with the enterically active components of the subcoat layer. The Bartoo et al. patent does not anticipate a delivery system that continuously

and osmotically interacts with the osmoresponsive component of the subcoat layer. Rather, the Bartoo et al. patent teaches a dosage form that self-regulates its permeability in response to external environmental conditions.

The Bartoo et al. dosage form requires the use of an acidic core formulation. This is required in order that the low pH internal to the dosage form causes the free carboxyl groups of the enteric components present within the subcoat layer to be protonated and therefore prevent the enteric polymer from dissolving. The low pH is retained even long after the last small crystal of solid drug has dissolved. The pH remains acidic as the drug solution becomes diluted by the water fluxing across the membrane into the dosage form. This is contrary to the mechanism of osmoresponsive membranes. The osmoresponsive membrane functions with acidic, neutral, and alkaline drugs. Moreover, the osmotic activity is directly proportional to the drug concentration according to van't Hoff's Law:

$$\Pi = iRTC/(MN)$$

where i represents number of ions per drug molecule, R represents gas constant, T represents temperature, C represents drug concentration, and MN represents drug molecular weight.

In osmotic systems having a single layer core, such as illustrated in our example with the drug metformin HCl, the concentration of drug within the delivery system the moment after the last solid crystal of drug has dissolved proceeds to decline parabolically with time. (Theeuwes, F. "Elementary Osmotic Pump", J. Pharm. Sci. Vol 64, No. 12, (December 1975)). Thus, while the Bartoo et al. dosage form undergoes minor changes in pH within the device as the acidic drug declines, the osmotic pressure of the dosage form declines precipitously and rapidly according to the parabolically declining osmotic pressure. The Bartoo et al. patent leads away from the use of this precipitous internal change in the osmotic system and does not anticipate it for use as a means to regulate permeability.

From the foregoing, it is clear that the Bartoo et al. patent does not anticipate or make obvious the invention recited in claims 46, 48, and 51-60. Withdrawal of the rejection of these claims over the Bartoo et al. patent is respectfully requested.

Conclusion

The rejected claims have been amended and/or shown to be allowable over the prior art. Applicants believe that this paper is fully responsive to each and every ground of rejection cited by the Examiner in the Office Action dated July 15, 2003, and respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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